

M142109 ENCL 7

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

D4

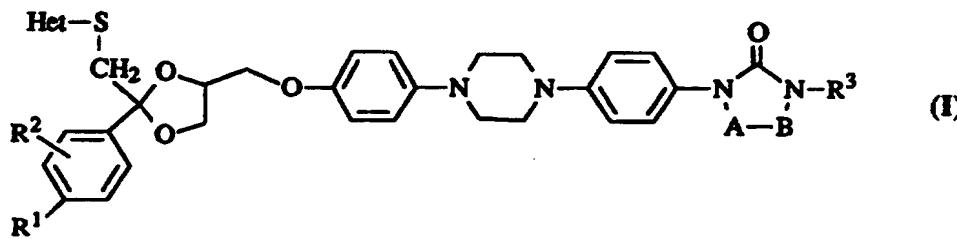
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 405/14, A61K 31/495		A1	(11) International Publication Number: WO 96/13499
			(43) International Publication Date: 9 May 1996 (09.05.96)
(21) International Application Number: PCT/EP95/04111			CKEN, Luc, Alfons, Leo [BE/BE]; Maurice Pottersstraat 12, B-2350 Vosselaar (BE). DE CHAFFOY DE COURCELLES, Didier, Robert, Guy, Gabriël [BE/BE]; Karel Van Nyenlaan 4, B-2340 Beerse (BE).
(22) International Filing Date: 19 October 1995 (19.10.95)			
(30) Priority Data: 94203120.4 27 October 1994 (27.10.94) EP (34) Countries for which the regional or international application was filed: 455,304 31 May 1995 (31.05.95) DE et al. US			(74) Agent: DE CORTE, Filip; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).
(60) Parent Application or Grant (63) Related by Continuation US 455,304 (CON) Filed on 31 May 1995 (31.05.95)			(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, HU, IS, JP, KE, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TT, UA, UG, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).
(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).			Published With international search report.
(72) Inventors; and (75) Inventors/Applicants (for US only): HEERES, Jan [NL/BE]; Leemskuil 18, B-2350 Vosselaar (BE). BACKX, Leo, Jacobus, Jozef [BE/BE]; Brookstraat 92, B-2370 Arendonk (BE). HENDRICKX, Robert, Jozef, Maria [BE/BE]; Sint-Corneliusstraat 60, B-2340 Beerse (BE). VAN DER EY-			

(54) Title: APOLIPOPROTEIN-B SYNTHESIS INHIBITORS

(57) Abstract

The present invention provides novel compounds of formula (I), the N-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts thereof, wherein A and B taken together form a bivalent radical of formula: -N-CH- (a), -CH=N- (b), -CH₂-CH₂- (c), -CH=CH- (d), -C(=O)-CH₂- (e), -CH₂-C(=O)- (f); R¹ is hydrogen, C₁-alkyl, or halo; R² is hydrogen or halo; R³ is hydrogen; C₁-alkyl; C₃-cycloalkyl or C₁-8 alkyl substituted with hydroxy, oxo, C₃-cycloalkyl or aryl. Het is five- or six membered optionally substituted heterocyclic ring. The use as a medicine, especially as a lipid lowering agent is disclosed as well as pharmaceutical compositions and processes for preparing compounds and compositions.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

APOLIPOPROTEIN-B SYNTHESIS INHIBITORS

The present invention concerns novel compounds of formula (I), pharmaceutical compositions comprising said compounds, the preparation thereof as well as the use as a medicine in the treatment of hyperlipidemia.

The causal relationship between hypercholesterolemia, particularly that associated with increased plasma concentrations of low density lipoproteins (LDL) and very low density

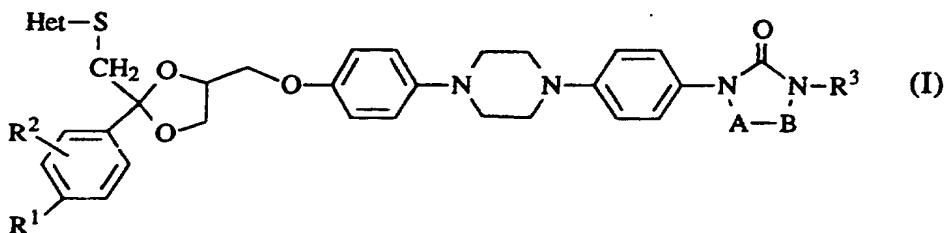
lipoprotein (VLDL) remnants, and premature atherosclerosis has gained widespread acceptance over the last few years. The consensus that treatment of hypercholesterolemia has therapeutic benefit has become widely accepted by both physicians and the public.

A limited number of drugs are available for the treatment of hyperlipidemia. The primary agents used for the management of hyperlipidemia included bile acid sequestrants, fibrates, nicotinic acid and HMG Co A-reductase inhibitors. The inconvenience of administration and gastro-intestinal side-effects of available bile acid sequestrants make compliance a major problem. The fibrates have only limited usefulness in the treatment for certain types of hypercholesterolemia. Treatment with nicotinic acid encompasses side-effects and toxicity problems. The HMG Co A-reductase inhibitors already form a first line treatment of familiar hypercholesterolemia. However there still remains a need for new lipid lowering agents for that act preferably via other mechanisms than the above mentioned drugs.

EP-0.006,711-A, published on September 9, 1980, discloses heterocyclic derivatives of (4-phenylpiperazin-1-yl-aryloxymethyl-1,3-dioxolan-2-yl)-methyl-1*H*-imidazoles and 1*H*-1,2,4-triazoles having antifungal properties. The presently claimed compounds differ therefrom by the presence of a sulfur atom adjacent to the Het-moiety and by their pharmacological profile, in particular their apolipoprotein B synthesis inhibiting activity.

The present invention provides novel compounds of formula

30



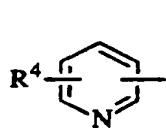
-2-

the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

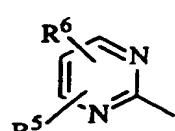
The heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C₁₋₆alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, 1-methylethyl, 2-methylpropyl and the like; C₁₋₈alkyl defines C₁₋₆alkyl and the higher homologues thereof containing 7 or 8 carbon atoms such as, for example, heptyl or octyl and the branched isomers thereof. C₃₋₆cycloalkyl defines saturated cyclic hydrocarbon radicals having from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

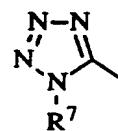
10 Het may in particular be a radical of formula



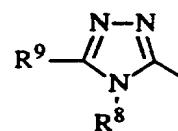
(a)



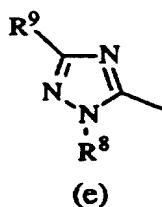
(b)



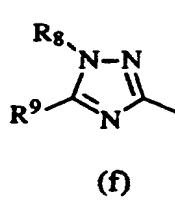
(c)



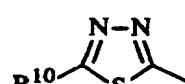
(d)



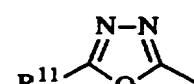
(e)



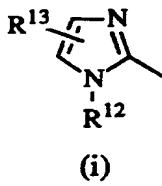
(f)



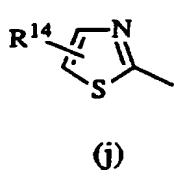
(g)



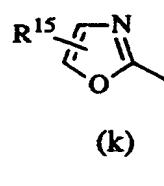
(h)



(i)



(j)



(k)

wherein :

15 R⁴ is hydrogen or C₁₋₆alkyl;
 R⁵ and R⁶ are hydrogen, C₁₋₆alkyl or amino;
 R⁷ is hydrogen or C₁₋₆alkyl;
 each R⁸ independently is hydrogen or C₁₋₆alkyl;
 each R⁹ independently is hydrogen, C₁₋₆alkyl, trifluoromethyl, amino or hydroxy;

20 R¹⁰ and R¹¹ each independently are hydrogen or C₁₋₆alkyl;
 R¹³ is hydrogen or C₁₋₆alkyl;
 R¹⁴ is hydrogen, C₁₋₆alkyl or hydroxy;
 R¹⁵ is hydrogen or C₁₋₆alkyl.

-4-

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for

5 example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric ; nitric ; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methane-sulfonic, ethanesulfonic, benzene-sulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like

10 acids. The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like. Conversely the salt form can be converted by treatment with alkali into the free base form.

15 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers

20 may have the R- or S-configuration; substituents on bivalent cyclic saturated radicals may have either the *cis*- or *trans*-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

25 The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more of the piperazine-nitrogens are *N*-oxidized.

30 The substituents on the dioxolane moiety of the compounds of formula (I) may have the *cis*- or *trans*-configuration. The compounds of formula (I) having the *cis*-configuration are preferred.

35 The compounds of formula (I) wherein the stereogenic carbon in the 2-position of the dioxolane moiety has the S-configuration are also preferred.

The compounds of formula (I) may also exist in their tautomeric forms. For instance, heterocycles such as, for example, pyridine, pyrimidine, triazole, thiadiazole, oxadiazole, imidazole, thiazole and oxazole, which are substituted with hydroxy, amino

-5-

or C₁-alkylamino may exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

5 A group of interesting compounds are those compounds of formula (I) wherein R¹ is chloro or fluoro, especially chloro.

Also a group of interesting compounds are those compounds of formula (I) wherein R¹ is C₁-alkyl, especially methyl.

10 10 A further group of interesting compounds are those compounds of formula (I) wherein R² is hydrogen, chloro or fluoro, preferably hydrogen.

Another group of interesting compounds of formula (I) are those compounds wherein 15 the bivalent radical -A-B- is -CH=CH-, -N=CH- or -CH=N-, especially -CH=N- or -N=CH-. In said bivalent radicals, the hydrogen atom may be replaced by C₁-alkyl, especially methyl.

20 A particular group of compounds are those compounds of formula (I) and especially those interesting compounds wherein R³ is C₁-8-alkyl or C₃-6-cycloalkyl, preferably butyl, pentyl or cyclopentyl.

25 A group of preferred compounds of formula (I) is formed by those compounds wherein Het is a triazole, substituted triazole, imidazole, substituted imidazole, thiazole, substituted thiazole.

30 More preferred compounds of formula (I) are those interesting or particular compounds wherein Het is 2-thiazolyl, 4-methyl-4H-1,2,4-triazol-3-yl, 4H-1,2,4-triazol-3-yl, 2-methyl-2H-1,2,4-triazol-3-yl or 2H-1,2,4-triazol-3-yl.

35 Most preferred compounds are
cis-4-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one;

40 *cis*-2-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(1-methyl-propyl)-3H-1,2,4-triazol-3-one;

cis-2-[4-[4-[[2-(4-fluorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4-cyclopentyl-2,4-dihydro-

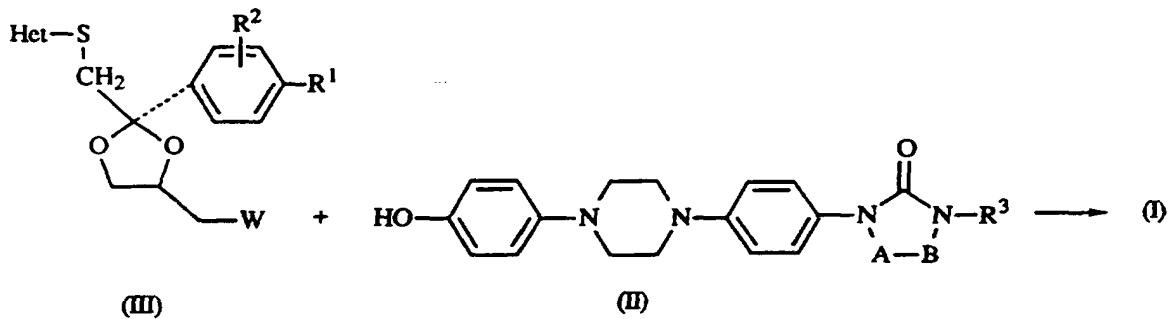
45 3H-1,2,4-triazol-3-one;

-6-

cis-2-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-pentyl-3H-1,2,4-triazol-3-one;

5 *cis*-4-(1-ethylpropyl)-2-[4-[4-[[2-(4-fluorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one; a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

10 The compounds of formula (I) may be prepared by *O*-alkylating a phenol of formula (II) with a 1,3-dioxolane derivative of formula (III), wherein W represents an appropriate leaving group such as halo, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. 4-methylbenzenesulfonyloxy (tosylate) or methanesulfonyloxy (mesylate).



15

Said *O*-alkylation reaction can conveniently be conducted following art-known procedures, e.g. by stirring and heating the reactants in an appropriate solvent such as a dipolar aprotic solvent, e.g. *N,N*-dimethylformamide, *N,N*-dimethylacetamide, in the presence of a base such as, an alkali metal hydroxide or carbonate, e.g. sodium or potassium hydroxide, or sodium or potassium carbonate.

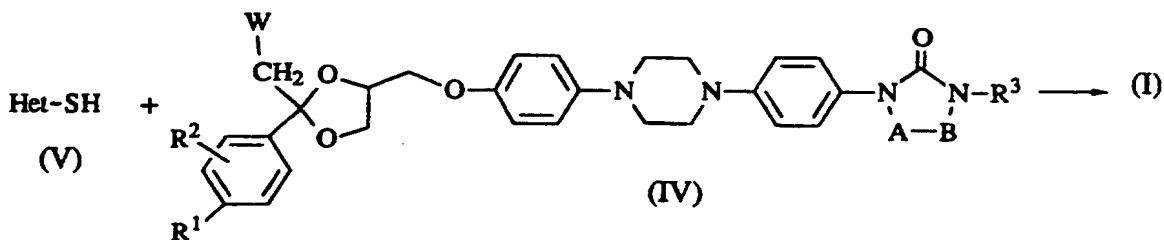
20

25 Intermediates of formula (II) may be prepared in similar ways as disclosed in EP-0,006,711, mentioned hereinabove. EP-0,331,232-A, published on September 6, 1989 and WO 93/19061, published on September 30, 1993, also disclose ways of preparing intermediates of formula (II).

30

The compounds of formula (I) may also be prepared by reacting an intermediate of formula (IV), wherein W is an appropriate leaving group as defined hereinabove with a heterocyclic derivative of formula (V).

-7-



Said reaction may be performed by stirring and heating the intermediates in an appropriate solvent such as a dipolar aprotic solvent, e.g. *N,N*-dimethylformamide, *N,N*-dimethyl-

5 acetamide, dimethylsulfoxide, in the presence of a base such as, an alkali metal carbonate or hydroxide, e.g. sodium or potassium carbonate, or sodium or potassium hydroxide.

Compounds of formula (I) may also be converted into each other.

10 For instance, the compounds wherein R^3 is C_{1-6} alkyl substituted with hydroxy may be prepared by reduction of the corresponding compounds of formula (I) wherein R^3 is C_{1-6} alkyl substituted with oxo. The compounds of formula (I) wherein an endocyclic or exocyclic nitrogen atom of the heterocyclic radical "Het" is substituted with a C_{1-6} alkyl may be prepared from the corresponding compounds wherein said endocyclic or

15 exocyclic nitrogen atom is unsubstituted by art-known *N*-alkylation reactions.

The compounds of formula (I) wherein R^3 is other than hydrogen may be prepared from compounds of formula (I) wherein R^3 is hydrogen by art-known *N*-alkylation reactions.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide

20 forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide.

Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate

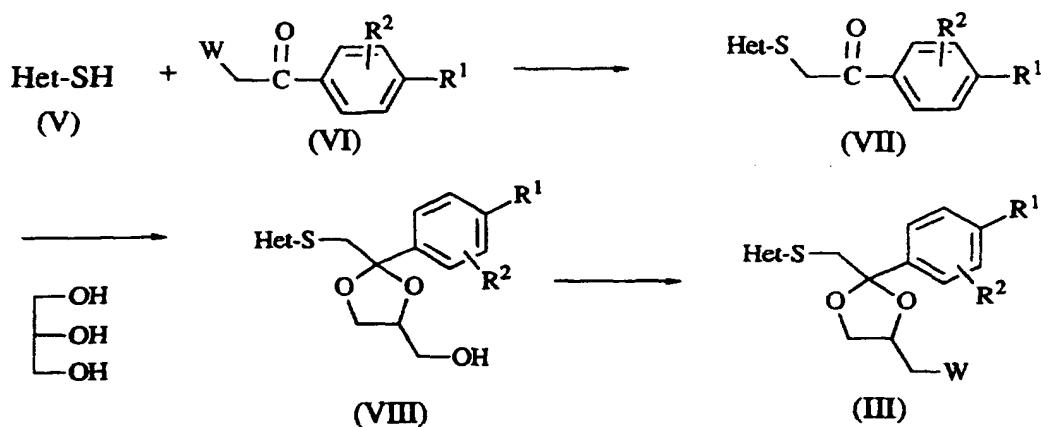
25 organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxyic acid or halo substituted benzenecarboperoxyic acid, e.g. 3-chlorobenzene-carbo-peroxyic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated

30 hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Intermediates of formula (III), which are deemed novel, may be prepared by the following reaction sequence. A heterocyclic reagent (V) is *S*-alkylated with an intermediate of formula (VI), wherein W is an appropriate leaving group as defined

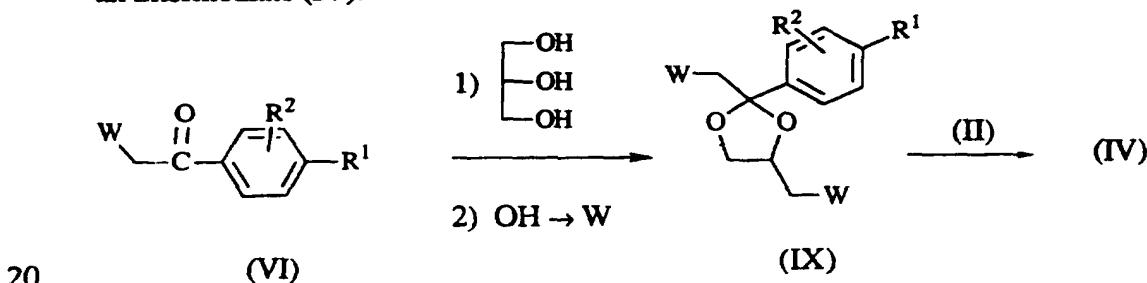
-8-

hereinabove, by stirring and heating the intermediates in an appropriate reaction-inert solvent such as a ketone, e.g. acetone, in the presence of a base such as a alkali metal carbonate or hydroxide, e.g. sodium or potassium carbonate, sodium or potassium hydroxide. The thus formed ketone of formula (VII) is then converted into the 5 corresponding ketal of formula (VIII) by stirring and heating the intermediate of formula (VII) with glycerol in the presence of an acid such as for example p-toluenesulfonic acid in a reaction inert solvent such as toluene. Finally, the hydroxylfunction of the intermediate of formula (VIII) is converted into an appropriate leaving group by art-known functional group transformation reations, such as, for example, converting the 10 hydroxyl group into a tosylate by reaction with p-toluenesulfonylchloride.



15 The intermediates of formula (IV) may be prepared be prepared in an analogous way.

An intermediate of formula (VI) is ketalized as described hereinabove. Subsequently, the hydroxyl function is converted into an appropriate leaving group, e.g. a sulfonyloxy group. Reaction of the thus formed intermediate (IX) with an intermediate (II) results in an intermediate (IV).



Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography. Enantiomers may be separated from each other 25

by forming diastereomeric salt forms with optically pure chiral acids and subsequent selective crystallization. Said pure stereochemically isomeric forms may also be prepared from the corresponding stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a 5 specific stereochemically isomeric form is desired, said form will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

10 The present compounds inhibit the synthesis of apolipoprotein B as can be evidenced by the results obtained in the "Apolipoprotein B (apo B) inhibition test" as described hereinafter. Apolipoprotein B is the principal protein component of very low density lipoproteins (VLDL) and low density lipoproteins (LDL). Approximately 60 to 70% of the total serum cholesterol is transported in LDL. Increased concentration of LDL-cholesterol in serum is causally related to atherosclerosis. By inhibiting the synthesis of 15 apolipoprotein B the amount of noxious low density lipoproteins is decreased.

20 The present compounds show no or little undesired side-effects such as, for example, albumine inhibiting activity, androgen biosynthesis inhibiting activity or cholesterol biosynthesis inhibiting activity.

25 In view of their apolipoprotein B inhibiting activity and concomitant lipid lowering activity the present compounds are useful as a medicine especially in a method of treating patients suffering from hyperlipidemia. In particular the present compounds may be used for the manufacture of a medicine for treating disorders caused by an excess of very low density lipoproteins (VLDL) or low density lipoproteins (LDL), and especially disorders caused by the cholesterol associated with said VLDL and LDL.

30 A large number of genetic and acquired diseases can result in hyperlipidemia. They can be classified into primary and secondary hyperlipidemic states. The most common causes of the secondary hyperlipidemias are diabetes mellitus, alcohol abuse, drugs, hypothyroidism, chronic renal failure, nephrotic syndrome, cholestasis and bulimia. Primary hyperlipidemias are common hypercholesterolaemia, familial combined hyperlipidaemia, familial hypercholesterolaemia, remnant hyperlipidaemia, chylomicronaemia syndrome, familial hypertriglyceridaemia. The present compounds may also be used to prevent or treat patients suffering from atherosclerosis, especially 35 coronary atherosclerosis and more in general disorders which are related to atherosclerosis, such as ischaemic heart disease, peripheral vascular disease, cerebral vascular disease. The present compounds may cause regression of atherosclerosis and inhibit the clinical consequences of atherosclerosis, particularly morbidity and mortality.

In view of their apolipoproteine B inhibiting activity the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare these pharmaceutical compositions, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is intimately mixed with a pharmaceutically acceptable carrier. Said carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of the compounds of formula (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable

-11-

solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Those of skill in the treatment of hyperlipidemia could easily determine the effective
5 daily amount from the test results presented hereinafter. In general it is contemplated
that a therapeutically effective dose would be from 0.001 mg/kg to 5 mg/kg body
weight, more preferably from 0.01 mg/kg to 0.5 mg/kg body weight. It may be
appropriate to administer the therapeutically effective dose as two, three, four or more
sub-doses at appropriate intervals throughout the day. Said sub-doses may be
10 formulated as unit dosage forms, for example, containing 0.05 mg to 250 mg, and in
particular 0.5 to 5 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound
15 of formula (I) used, the particular condition being treated, the severity of the condition
being treated, the age, weight and general physical condition of the particular patient as
well as other other medication the patient may be taking, as is well known to those
skilled in the art. Furthermore, it is evident that said effective daily amount may be
lowered or increased depending on the response of the treated patient and/or depending
on the evaluation of the physician prescribing the compounds of the instant invention.
20 The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Experimental part

Hereinafter, the term "DIPE" means diisopropylether, "MIK" means methylisopropyl
25 ketone and "DMF" means *N,N*-dimethylformamide.

A. Preparation of the intermediates

Example 1

a) A mixture of 1-methyl-1*H*-1,2,4-triazole-5-thiol (35 g), 2-chloro-1-(fluorophenyl)-
30 ethanone (51.4 g) and sodium carbonate (32.5 g) in 2-propanone (500 ml) was stirred
and refluxed for 4 hours. The solvent was evaporated, the residue was dissolved in
CH₂Cl₂, filtered and the filtrate evaporated. The residue was crystallized from DIPE,
yielding 25 g (33%) of product. A sample (3 g) was purified by column
chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions
35 were collected and evaporated. The residue was crystallized from DIPE, yielding 1-(4-
fluorophenyl)-2-[(2-methyl-2*H*-1,2,4-triazol-3-yl)thio]ethanone (interm. 1).
b) A mixture of intermediate (1) (22 g), glycerol (39.6 g) and *p*-toluenesulfonic acid
(20 g) in toluene (200 ml) was stirred and refluxed overnight. The mixture was cooled
and water was added. The mixture was extracted with toluene and washed with water.

-12-

The organic layer was dried, filtered and the solvent evaporated. The residue was purified by HPLC over silica gel (eluent : $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2). The pure fractions were collected and evaporated, yielding 9 g (31.6%) of (\pm) -*cis*-2-(4-fluorophenyl)-2-[[$(2\text{-methyl-2H-1,2,4-triazol-3-yl})$ thio]methyl]-1,3-dioxolane-4-methanol (interm. 2).

5 c) A mixture of intermediate (2) (9 g), *p*-toluene sulfonyl chloride (6.3 g) and *N,N*-dimethyl-4-pyridinamine (1 g) in CH_2Cl_2 (150 ml) and *N,N*-diethylethanamine (5 ml) was stirred at room temperature for 4 hours. Water was added and the layers were separated. The organic layer was washed with water, dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1). The pure fractions were collected and evaporated at a temperature $< 35^\circ\text{C}$. The residue was dissolved in MIK and converted into the *p*-toluenesulfonic acid salt (1:1). A little DIPE was added and the product was crystallized out. The precipitate was filtered off and dried, yielding 6.8 g (37.8%) of (\pm) -*cis*-2-(4-fluorophenyl)-2-[[$(2\text{-methyl-2H-1,2,4-triazol-3-yl})$ thio]methyl]-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate 4-methylbenzenesulfonate(1:1) (interm. 3).

10 In a similar manner were also prepared :
 (\pm) -*cis*-2-(4-fluorophenyl)-2-[[$(4\text{-methyl-4H-1,2,4-triazol-3-yl})$ thio]methyl]-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate(ester) 4-methylbenzenesulfonate(1:1);
20 mp. 136.4°C (interm. 4);
 (\pm) -*cis*-2-(2,4-difluorophenyl)-2-[[$(4\text{-methyl-4H-1,2,4-triazol-3-yl})$ thio]methyl]-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate(ester) 4-methylbenzenesulfonate (1:1) (interm. 5);
 (\pm) -*trans*-2-(4-chlorophenyl)-2-[[$(4\text{-methyl-4H-1,2,4-triazol-3-yl})$ thio]methyl]-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate(ester) 4-methylbenzenesulfonate (1:1); mp. 151.9°C (interm. 6);
 (\pm) -*cis*-2-(2,4-difluorophenyl)-2-[[$(2\text{-methyl-2H-1,2,4-triazol-3-yl})$ thio]methyl]-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate (ester) (interm. 7); and
 (\pm) -*cis*-[2-(bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl
2-naphthalenesulfonate (interm. 40).

25 30

Example 2

a) A mixture of 2-bromo-1-(4-chlorophenyl)ethanone (350 g), glycerine (322 g) and *p*-toluenesulfonic acid (35 g) in toluene (3000 ml) was stirred and refluxed for 24 hours, using a water separator. The reaction mixture was poured into an aqueous NaHCO_3 solution and stirred for a while. The organic layer was separated, dried,

35

-13-

filtered and the solvent was evaporated, yielding 485 g (93%; oil) of (*cis* +*trans*)-2-(bromomethyl)-2-(4-chlorophenyl)-1,3-dioxolane-4-methanol (interm. 8a).

2-Naphthalenesulfonyl chloride (21 g) was added portionwise to a mixture of intermediate (8a) (25 g) and *N,N*-dimethyl-4-pyridinamine (1 g) in *N,N*-diethylethanamine

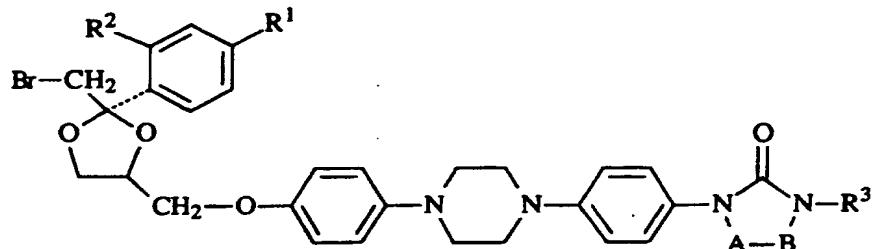
5 (25 ml) and CH₂Cl₂ (250 ml) and the mixture was stirred at room temperature for 2 hours. The mixture was poured into water and washed. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was purified by column chromatography (eluent : CH₂Cl₂/hexane 40/60 to 60/40). The pure fractions were collected and evaporated, yielding 21.8 g (55%) of (\pm)-*cis*-[2-(bromomethyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl 2-naphthalenesulfonate (interm. 8b).

10 c) 2,4-dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (206.9 g) was added to a solution of intermediate (8b) (250 g) in 15 dimethyl sulfoxide (2000 ml). Potassium hydroxide (67 g) was added and the reaction mixture was stirred overnight at room temperature. The mixture was poured into water (3000 ml) and stirred for 30 minutes. The precipitate was filtered off, washed with 2-propanol (1000 ml) and DIPE (1000 ml), then dried, yielding 316 g (92.2%) of (\pm)-*cis*-4-[4-[4-[2-(bromomethyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methoxy]-20 phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (interm. 8c).

In a similar manner were prepared :

Table 1

25



Int. No.	R ¹	R ²	A-B	R ³	Physical data
8c	Cl	H	CH=N	CH(CH ₃)CH ₂ CH ₃	<i>cis</i>
9	Cl	H	N=CH	CH(CH ₃) ₂	mp. 185.8°C; <i>cis</i>
10	Cl	H	CH=N	CH ₂ CH(CH ₃) ₂	mp. 168.3°C; <i>cis</i>
11	Cl	H	N=CH	CH ₂ CH(CH ₃) ₂	mp. 175.6°C; <i>cis</i>
12	Cl	H	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 172.6°C; <i>cis</i>

Int. No.	R ¹	R ²	A-B	R ³	Physical data
13	Cl	H	N=CH	CH(CH ₂ CH ₃) ₂	mp. 164.3°C; <i>cis</i>
14	Cl	H	N=CH	(CH ₂) ₂ CH ₃	mp. 201.9°C; <i>cis</i>
15	Cl	H	N=CH	(CH ₂) ₃ CH ₃	mp. 153.8°C; <i>cis</i>
16	Cl	H	CH=N	cycloC ₅ H ₉	<i>cis</i>
17	Cl	H	CH=N	(CH ₂) ₃ CH ₃	mp. 172.0°C; <i>cis</i>
18	Cl	H	N=CH	CH ₂ CH ₃	mp. 186.3°C; <i>cis</i>
19	Cl	H	N=CH	(CH ₂) ₄ CH ₃	mp. 164.7°C; <i>cis</i>
20	Cl	H	CH=N	(CH ₂) ₂ CH ₃	mp. 172.9°C; <i>cis</i>
21	Cl	H	CH=N	CH ₂ CH ₃	mp. 186.6°C; <i>cis</i>
22	Cl	H	N=CH	CH ₃	mp. 203.9°C; <i>cis</i>
23	Cl	H	CH=N	CH ₃	<i>cis</i>
24	Cl	H	CH=N	CH(CH ₃)CH ₂ CH ₃	[2S-[2 α ,4 α (R*)]]
25	Cl	H	CH=N	CH(CH ₃)CH ₂ CH ₃	[2R-[2 α ,4 α (S*)]]
26	Cl	H	CH=N	CH(CH ₃)CH ₂ CH ₃	[2S-[2 α ,4 α (S*)]]
27	Cl	H	CH=N	CH(CH ₃)CH ₂ CH ₃	[2R-[2 α ,4 α (R*)]]
28	F	H	CH=N	(CH ₂) ₂ CH(CH ₃) ₂	mp. 170.3°C; <i>cis</i>
29	F	H	CH=N	CH(CH ₂ CH ₃) ₂	<i>cis</i>
30	F	H	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 152.9°C; <i>cis</i>
31	F	H	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 174.2°C; <i>cis</i>
32	F	F	CH=N	CH(CH ₂ CH ₃) ₂	<i>cis</i>
33	Cl	H	C(CH ₃) ₂ CO	CH(CH ₃)CH ₂ CH ₃	<i>cis</i>
34	Cl	H	COC(CH ₃) ₂	CH(CH ₃)CH ₂ CH ₃	<i>cis</i>
35	Cl	H	C(CH ₃)=N	CH(CH ₃)CH ₂ CH ₃	<i>cis</i>
36	F	H	CH=N	cycloC ₅ H ₉	<i>cis</i>
37	F	H	N=CH	cycloC ₅ H ₉	<i>cis</i>
38	F	H	N=CH	CH(CH ₂ CH ₃) ₂	<i>cis</i>
39	F	F	CH=N	cycloC ₅ H ₉	<i>cis</i>
40	F	H	CH=CH	CH(CH ₃)CH ₂ CH ₃	<i>cis</i>
41	Cl	H	CH=CH	CH(C ₂ H ₅)CH ₂ CH ₃	mp. 169.8°C; <i>cis</i>
42	Cl	H	CH=CH	cycloC ₅ H ₉	mp. 192.7°C; <i>cis</i>
43	F	H	N=CH	(CH ₂) ₄ CH ₃	<i>cis</i>
44	Cl	H	N=CH	cycloC ₅ H ₉	mp. 192.3°C; 2S- <i>cis</i>
45	Cl	H	N=CH	(CH ₂) ₄ CH ₃	2S- <i>cis</i>

B. Preparation of the final compounds**Example 3**

A mixture of 4-methyl-4*H*-1,2,4-triazole-3-thiol (1.9 g), intermediate (8c) (9 g) and sodium carbonate (3 g) in DMF (150 ml) was stirred under N₂ at 120°C overnight. The 5 mixture was cooled, diluted with water and the product was crystallized out. The precipitate was filtered off and purified by column chromatography over silica gel (eluent : CH₂Cl₂/n-hexane/EtOAc/CH₃OH 500/250/250/2). The pure fractions were collected and evaporated. The residue was triturated in CH₃OH and recrystallized from 10 n-C₄H₉OH, yielding 6.3 g of (±)-*cis*-4-[4-[4-[2-(4-chlorophenyl)-2-[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (68%); mp. 173°C (compound 22).

Example 4

15 A mixture of intermediate (3) (3.3 g), 2,4-dihydro-2-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-4-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (2 g) and potassium hydroxide (1 g) in DMF (100 ml) was stirred at room temperature under N₂ for 6 hours. Intermediate (3) (1 g) was added again and the mixture was stirred for 1 hour. The mixture was poured into water and filtered. The precipitate was purified by column 20 chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and evaporated. The residue was crystallized from MIK, yielding 1.6 g of (±)-*cis*-2-[4-[4-[4-[2-(4-fluorophenyl)-2-[(2-methyl-2*H*-1,2,4-triazol-3-yl)thio]-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (45.7%); mp. 157.3°C (compound 70).

25

Example 5

Sodium hydride, 50%, dispersion in mineral oil (0.31 g) was added to a mixture 30 of compound (76) (4.3 g) in DMF (100 ml) and the mixture was stirred at room temperature for 30 minutes. 2-Bromopropane (0.86 g) was added and the mixture was stirred at room temperature for 48 hours. Sodium hydride, 50%, dispersion in mineral oil and 2-bromopropane were added again and the mixture was stirred for 4 hours. The mixture was poured into water, extracted with CH₂Cl₂ and washed with water. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure 35 fractions were collected and evaporated. The residue was crystallized from CH₃OH. The residue was purified by HPLC. The pure fractions were collected and evaporated. Fraction 1 was crystallized from n-C₄H₉OH, yielding 0.4 g of (±)-*cis*-4-[4-[4-[2-(4-chlorophenyl)-2-[[1-(1-methylethyl)-1*H*-1,2,4-triazol-3-yl]thio]methyl]-1,3-

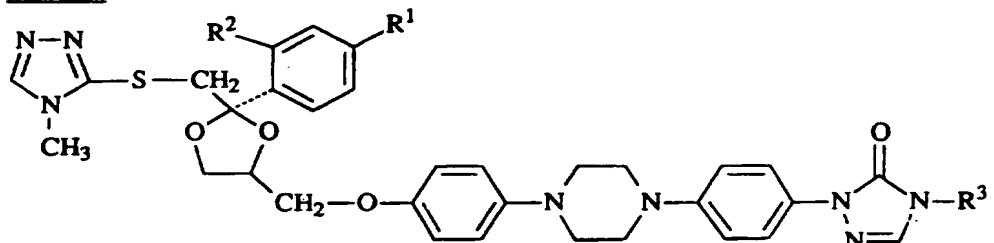
-16-

dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; mp. 128.8°C (compound 112). Fraction 2 was triturated in CH₃OH, yielding 1.4 g of (\pm)-*cis*-4-[4-[4-[2-(4-chlorophenyl)-2-[[2-(1-methylethyl)-2*H*-1,2,4-triazol-3-yl]thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; mp. 141.2°C (compound 82).

Example 6

A solution of sodium borohydride (1 g) in water (20 ml) was added dropwise to a 10 solution of compound (47) (3.6 g) in DMF (100 ml). The reaction mixture was stirred overnight at room temperature. Acetic acid (1 ml) was added. Water (750 ml) was added, resulting in crystallization of the product. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue was triturated in 15 2-propanol. The precipitate was filtered off and dried, yielding 2.9 g of (\pm)-*cis*-4-[4-[4-[2-(4-chlorophenyl)-2-[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(2-hydroxy-1-methylpropyl)-3*H*-1,2,4-triazol-3-one; mp. 153.4°C (compound 48).

20 Table 2

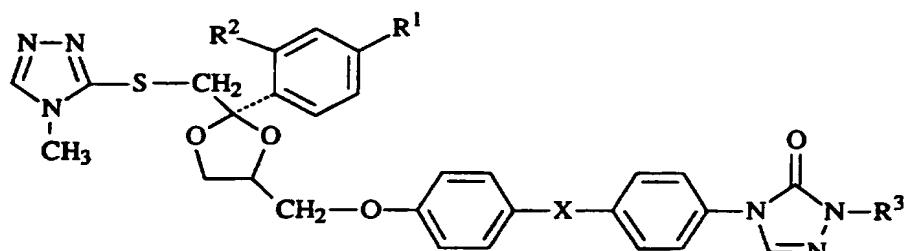


Co. No	Ex. No.	R ¹	R ²	R ³	physical data
1	3	Cl	H	CH(CH ₃) ₂	mp. 194.8°C / <i>cis</i>
2	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	mp. 147.8°C / <i>cis</i>
3	3	Cl	H	CH ₂ -CH(CH ₃) ₂	mp. 182.5°C / <i>cis</i>
4	4	F	H	CH(CH ₃) ₂	mp. 181.1°C / <i>cis</i>
5	4	F	H	CH ₂ -CH(CH ₃) ₂	mp. 166.4°C / <i>cis</i>
6	3	Cl	H	cyclo(C ₅ H ₉)	mp. 198.8°C / <i>cis</i>
7	3	Cl	H	CH(CH ₂ CH ₃) ₂	mp. 139.6°C / <i>cis</i>
8	3	Cl	H	(CH ₂) ₂ CH ₃	mp. 184.6°C / <i>cis</i>
9	4	F	H	CH(CH ₃)CH ₂ CH ₃	mp. 180.0°C / <i>cis</i>
10	4	F	F	CH(CH ₃)CH ₂ CH ₃	mp. 180.7°C / <i>cis</i>

-17-

Co. No	Ex. No.	R ¹	R ²	R ³	physical data
11	4	F	H	cyclo(C ₅ H ₉)	mp. 194.2°C / <i>cis</i>
12	4	F	H	CH(CH ₂ CH ₃) ₂	mp. 144.3°C / <i>cis</i>
13	4	F	F	cyclo(C ₅ H ₉)	mp. 202.4°C / <i>cis</i>
14	4	F	F	CH(CH ₂ CH ₃) ₂	mp. 166.7°C / <i>cis</i>
15	3	Cl	H	(CH ₂) ₃ CH ₃	mp. 194.6°C / <i>cis</i>
16	3	Cl	H	CH ₂ -CH ₃	mp. 218.3°C / <i>cis</i>
17	3	Cl	H	CH ₂ -CH(OH)-C(CH ₃) ₃	mp. 205.9°C / <i>cis</i>
18	3	Cl	H	(CH ₂) ₄ CH ₃	mp. 173.8°C / <i>cis</i>
19	4	Cl	H	CH(CH ₃)CH ₂ CH ₃	mp. 140.9°C / <i>trans</i>
20	4	Cl	H	CH ₃	mp. 208.6°C / <i>cis</i>
21	4	Cl	H	CH(CH ₃)CH(OH)(CH ₃)	mp. 202.4°C / <i>cis</i>
133	3	CH ₃	H	(CH ₂) ₄ CH ₃	mp. 147.4°C / <i>cis</i>
134	3	Br	H	(CH ₂) ₄ CH ₃	mp. 152.5°C / <i>cis</i>
136	3	Cl	H	cyclo(C ₅ H ₉)	2S- <i>cis</i>
137	3	Cl	H	(CH ₂) ₄ CH ₃	2S- <i>cis</i>

Table 3



5

Co. No	Ex. No.	R ¹	R ²	R ³	-X-	physical data
22	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N—Cyclohexyl—	mp. 176.9°C / <i>cis</i>
23	3	Cl	H	CH ₂ CH(CH ₃) ₂	—N—Cyclohexyl—	mp. 192.9°C / <i>cis</i>
24	3	Cl	H	cyclo(C ₅ H ₉)	—N—Cyclohexyl—	mp. 210.2°C / <i>cis</i>
25	4	F	H	CH ₂ CH(CH ₃) ₂	—N—Cyclohexyl—	mp. 180.6°C / <i>cis</i>
26	3	Cl	H	(CH ₂) ₃ CH ₃	—N—Cyclohexyl—	mp. 194.1°C / <i>cis</i>

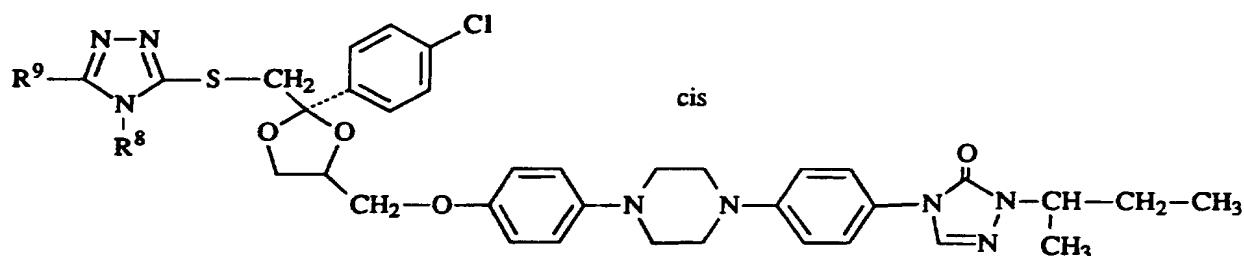
-18-

Co. No	Ex. No.	R ¹	R ²	R ³	-X-	physical data
27	3	Cl	H	(CH ₂) ₂ CH ₃	—N— C C C N—	mp. 187.3°C / <i>cis</i>
28	4	F	H	CH(CH ₃)CH ₂ CH ₃	—N— C C C N—	mp. 157.5°C / <i>cis</i>
29	4	F	F	CH(CH ₃)CH ₂ CH ₃	—N— C C C N—	mp. 146.4°C / <i>cis</i>
30	3	Cl	H	CH ₂ -CH ₃	—N— C C N—	mp. 195.5°C / <i>cis</i>
31	3	Cl	H	CH ₃	—N— C C N—	mp. 161.2°C / <i>cis</i>
32	4	Cl	H	(CH ₂) ₄ CH ₃	—N— C C C N—	mp. 191.7°C / <i>cis</i>
33	4	Cl	H	CH(CH ₃) ₂	—N— C C N—	mp. 157.2°C / <i>cis</i>
34	4	Cl	H	CH ₂ -CH(OH)-C(CH ₃) ₃	—N— C C N—	mp. 189.9°C / <i>cis</i>
35	4	F	H	cyclo(C ₅ H ₉)	—N— C C N—	mp. 198.2°C / <i>cis</i>
36	4	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N— C C N—	mp. 180.7°C / <i>trans</i>
37	4	F	F	cyclo(C ₅ H ₉)	—N— C C N—	mp. 185.2°C / <i>cis</i>
38	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N— C C N—	mp. 187.0°C / [α] _D ²⁰ = -24.5° (c = 0.5% in DMF) (-)-[2S-[2α,4α(R*)]]
39	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N— C C N—	mp. 155.1°C / [α] _D ²⁰ = +34.64° (c = 0.5% in DMF) (+)-[2R-[2α,4α(S*)]]
40	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N— C C N—	mp. 156.4°C /[α] _D ²⁰ = -33.1° (c = 0.5% in DMF) (-)-[2S-[2α,4α(S*)]]
41	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N— C C N—	mp. 187.7°C / [α] _D ²⁰ = +24.65° (c = 0.5% in DMF) (+)-[2R-[2α,4α(R*)]]
42	3	F	H	(CH ₂) ₂ CH(CH ₃) ₂	—N— C C N—	mp. 176.4°C / <i>cis</i>

-19-

Co. No	Ex. No.	R ¹	R ²	R ³	-X-	physical data
43	3	F	H	CH(CH ₂ CH ₃) ₂	—N— Cyclohexyl	mp. 145.6°C / <i>cis</i>
44	4	Cl	H	CH(CH ₂ CH ₃) ₂	—N— Cyclohexyl	mp. 156.7°C / <i>cis</i>
45	4	F	F	(CH ₂) ₂ CH(CH ₃) ₂	—N— Cyclohexyl	mp. 176.8°C / <i>cis</i>
46	3	F	F	CH(CH ₂ CH ₃) ₂	—N— Cyclohexyl	mp. 118.6°C / <i>cis</i>
47	4	Cl	H	CH(CH ₃)COCH ₃	—N— Cyclohexyl	mp. 157.6°C / <i>cis</i>
48	6	Cl	H	CH(CH ₃)CH(OH)CH ₃	—N— Cyclohexyl	mp. 153.4°C / <i>cis</i>
135	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	—N— Cyclohexyl	<i>cis</i>

Table 4

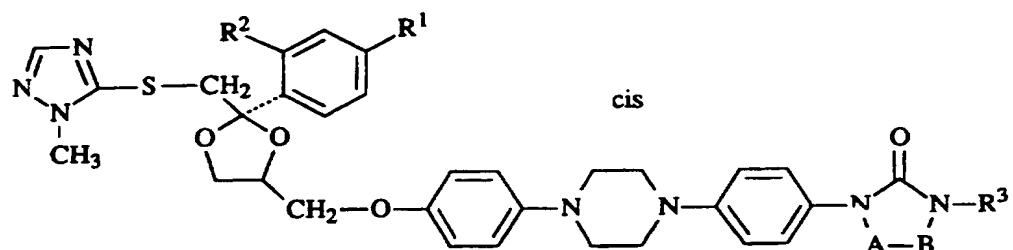


5

Co. No.	Ex. No.	R ⁹	R ⁸	physical data
49	3	CF ₃	H	mp. 133.3°C
50	3	CF ₃	CH ₃	mp. 159.6°C
51	3	H	(CH ₂) ₃ CH ₃	mp. 173.5°C
52	3	H	CH(CH ₃) ₂	mp. 159.1°C
53	3	H	CH ₂ CH ₃	mp. 175.6°C
54	3	H	CH ₂ CH(CH ₃) ₂	mp. 186.4°C
55	3	H	(CH ₂) ₂ CH ₃	mp. 168.5°C
56	3	CH ₃	CH ₃	mp. 170.0°C
57	3	NH ₂	H	-
58	3	OH	CH ₃	-
59	3	OH	CH(CH ₃) ₂	-

-20-

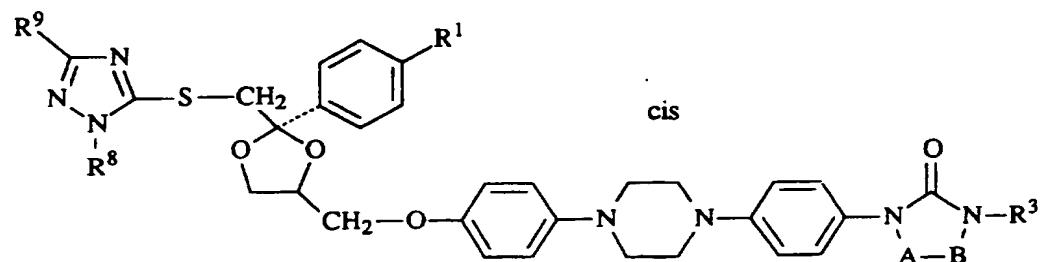
Table 5



Co. No.	Ex. No.	R ¹	R ²	R ³	A-B	physical data
60	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	CH=N	mp. 147.7°C
61	3	Cl	H	CH ₂ CH(CH ₃) ₂	CH=N	mp. 159.4°C
62	4	F	F	CH(CH ₃)CH ₂ CH ₃	CH=N	mp. 100.6°C
63	4	F	H	CH(CH ₃)CH ₂ CH ₃	CH=N	mp. 138.8°C
64	3	F	H	CH(CH ₂ CH ₃) ₂	CH=N	mp. 132.3°C
65	3	F	F	CH(CH ₂ CH ₃) ₂	CH=N	mp. 120.4°C
66	3	F	H	cyclo(C ₅ H ₉)	CH=N	mp. 163.0°C
67	3	F	F	cyclo(C ₅ H ₉)	CH=N	mp. 150.7°C
68	3	Cl	H	CH(CH ₃) ₂	N=CH	mp. 170.1°C
69	3	Cl	H	CH(CH ₃)CH ₂ CH ₃	N=CH	mp. 176.2°C
70	4	F	H	CH(CH ₃)CH ₂ CH ₃	N=CH	mp. 157.3°C
71	4	F	F	CH(CH ₃)CH ₂ CH ₃	N=CH	mp. 162.4°C
72	4	F	F	cyclo(C ₅ H ₉)	N=CH	mp. 183.3°C
73	4	F	F	CH(CH ₂ CH ₃) ₂	N=CH	mp. 158.9°C
74	3	F	H	cyclo(C ₅ H ₉)	N=CH	mp. 201.2°C
75	3	F	H	CH(CH ₂ CH ₃) ₂	N=CH	mp. 117.4°C

5

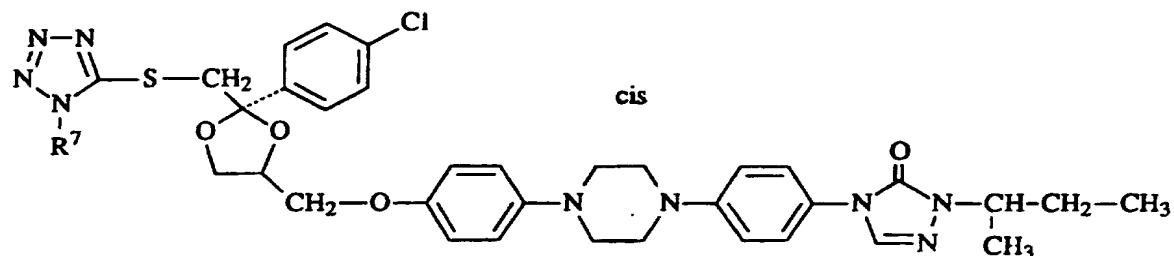
Table 6



-21-

Co. No.	Ex. No.	R ⁹	R ⁸	R ¹	A-B	R ³	physical data
76	3	H	H	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 179.6°C
77	3	H	CH ₂ CH ₃	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 119.3°C
78	3	CH ₂ CH ₃	(CH ₂) ₂ CH ₃	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 97.8°C
79	3	H	(CH ₂) ₃ CH ₃	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 108.6°C
80	3	H	(CH ₂) ₂ CH ₃	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 87.3°C
81	3	CH ₃	CH ₃	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 85.6°C
82	5	H	CH(CH ₃) ₂	Cl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 141.2°C
83	3	H	H	Cl	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 160.1°C
84	3	H	H	Cl	N=CH	CH ₂ CH(CH ₃) ₂	mp. 160.6°C
85	5	H	CH(CH ₃) ₂	Cl	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 134.9°C
86	3	H	H	F	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 101.3°C
87	3	H	CH ₃	Cl	N=CH	CH ₂ CH(CH ₃) ₂	mp. 154.3°C
114	3	H	CH ₃	Cl	CH=CH	CH(CH ₃)CH ₂ CH ₃	mp. 125.2°C
115	3	H	CH ₃	Cl	CH=CH	CH(C ₂ H ₅)CH ₂ CH ₃	mp. 147.7°C
116	3	H	CH ₃	Cl	CH=CH	cyclo(C ₅ H ₉)	mp. 154.2°C
117	3	H	H	Cl	CH=CH	CH(CH ₃)CH ₂ CH ₃	mp. 186.8°C
118	3	H	CH ₃	F	CH=CH	CH(C ₂ H ₅)CH ₂ CH ₃	mp. 134.1°C
119	3	H	CH ₃	Cl	CH=N	cyclo(C ₅ H ₉)	mp. 161.1°C
120	5	H	CH(CH ₃) ₂	Cl	CH=CH	CH(CH ₃)CH ₂ CH ₃	mp. 137.5°C
121	3	H	CH ₃	F	CH=CH	cyclo(C ₅ H ₉)	mp. 166.2°C

Table 7

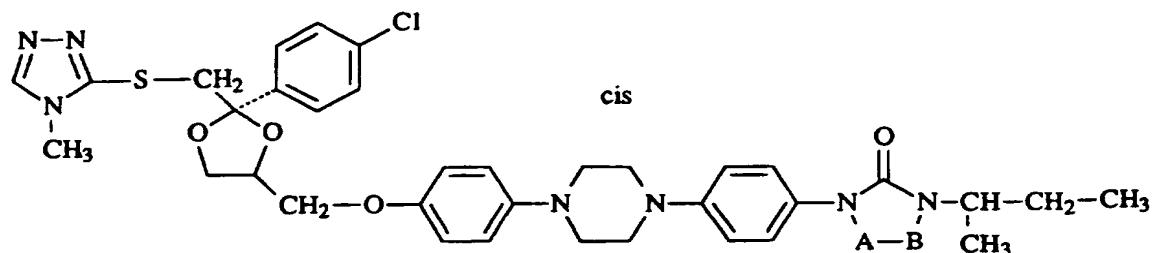


5

Co. No.	Ex. No.	R ⁷	physical data
88	3	CH ₃	-
89	3	phenyl	-

-22-

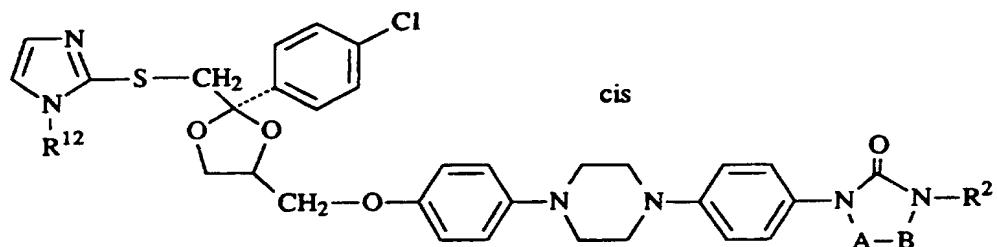
Table 8



5

Co. No.	Ex. No.	A-B	physical data
90	3	$\text{C}(\text{CH}_3)=\text{N}$	mp. 98.3°C / 1/2 H_2O
91	3	$\text{C}(\text{CH}_3)_2\text{CO}$	mp. 96.0°C
92	3	$\text{CO}-\text{C}(\text{CH}_3)_2$	mp. 127.1°C
93	4	$\text{CH}=\text{CH}$	mp. 171.8°C
94	4	CH_2-CH_2	mp. 147.3°C

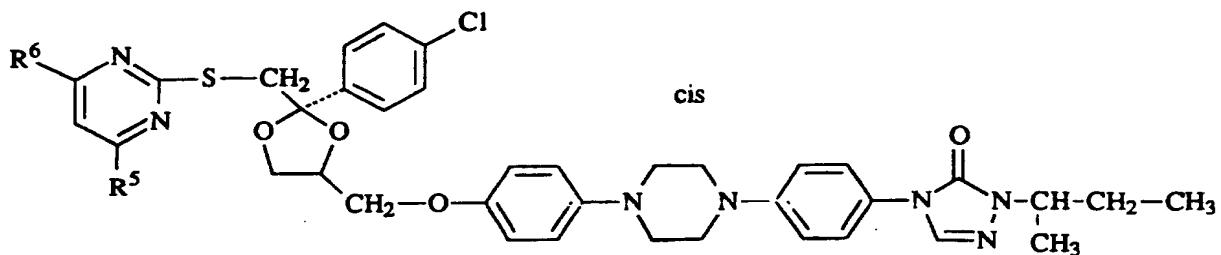
Table 9



10

Co. No.	Ex. No.	R ¹²	A-B	R ²	physical data
95	3	CH ₃	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 134.2°C
96	3	CH ₃	CH=N	CH ₂ CH(CH ₃) ₂	mp. 164.9°C
97	3	H	CH=N	CH(CH ₃)CH ₂ CH ₃	-
98	3	CH ₃	N=CH	CH(CH ₃) ₂	mp. 187.7°C
99	3	CH ₃	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 150.4°C
100	3	CH ₃	N=CH	CH ₂ CH(CH ₃) ₂	mp. 146.8°C

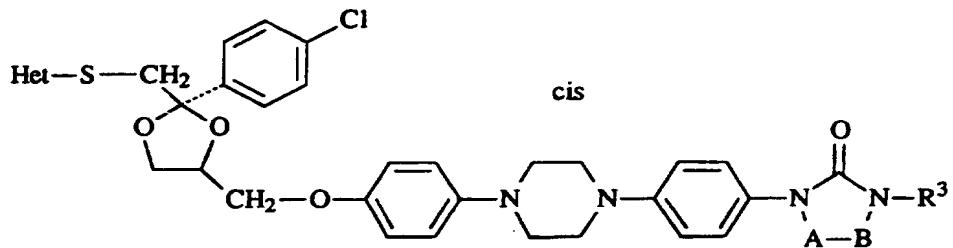
Table 10



Co. No.	Ex. No.	R ⁵	R ⁶	physical data
101	3	H	H	mp. 159.6°C
102	3	CH ₃	CH ₃	mp. 157.4°C
103	3	NH ₂	NH ₂	mp. 248.5°C

5

Table 11

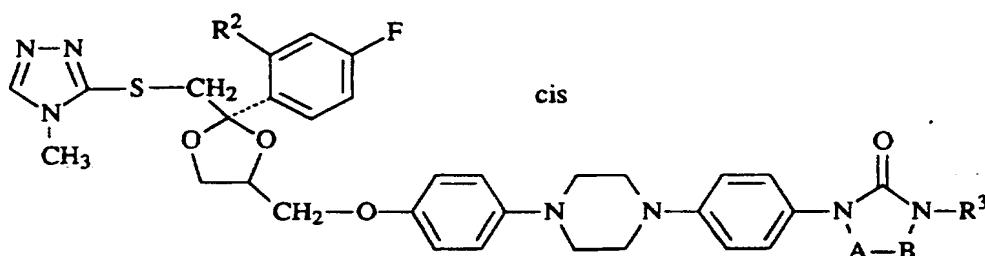


Co. No.	Ex. No.	Het	A-B	R ³	physical data
104	3	5-methyl-1,3,4-thia diazol-2-yl	CH=N	CH(CH ₃)CH ₂ CH ₃	-
105	3	2-pyridinyl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 154.1°C
106	3	4-pyridinyl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 174.9°C
107	3	4-methyl-2-oxazolyl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 115.3°C
108	3	2-thiazolyl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 158.6°C
109	3	4-oxo-2-thiazolyl	CH=N	CH(CH ₃)CH ₂ CH ₃	-
110	3	2-thiazolyl	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 157.8°C
111	3	2-thiazolyl	N=CH	CH ₂ CH(CH ₃) ₂	mp. 167.9°C
112	5	(1-methylethyl)-2 <i>H</i> -1,2,4-triazol-3-yl	CH=N	CH(CH ₃)CH ₂ CH ₃	mp. 128.8°C
113	5	(1-methylethyl)-1 <i>H</i> -1,2,4-triazol-3-yl	N=CH	CH(CH ₃)CH ₂ CH ₃	mp. 150.0°C
122	3	4-methyl-4 <i>H</i> -1,2,4-triazol-3-yl	CH=CH	CH(C ₂ H ₅)CH ₂ CH ₃	mp. 134.4°C

-24-

Co. No.	Ex. No.	Het	A-B	R ³	physical data
123	3	4-methyl-4H-1,2,4-triazol-3-yl	CH=CH	cyclo(C ₅ H ₉)	mp. 202.8°C
124	5	(1-methylethyl)-1H-1,2,4-triazol-3-yl	CH=CH	CH(CH ₃)CH ₂ CH ₃	mp. 155.7°C
125	3	4-methyl-4H-1,2,4-triazol-3-yl	CH=N	CH(C ₂ H ₅)CH ₂ CH ₃	mp. 123.2°C

Table 12



5

Co. No.	Ex. No.	R ²	R ³	A-B	physical data
126	3	H	CH(CH ₃)CH ₂ CH ₃	CH=CH	mp. 175.4°C
127	3	F	CH(CH ₃)CH ₂ CH ₃	CH=CH	mp. 155.5°C
128	3	H	cyclo(C ₅ H ₉)	CH=CH	mp. 192.0°C
129	3	F	cyclo(C ₅ H ₉)	CH=CH	mp. 181.8°C
130	3	H	CH(C ₂ H ₅)CH ₂ CH ₃	CH=CH	mp. 145.5°C
131	3	F	CH(C ₂ H ₅)CH ₂ CH ₃	CH=CH	mp. 139.1°C
132	3	H	(CH ₂) ₄ CH ₃	N=CH	mp. 153.1°C

C. Pharmacological exampleExample 7: Apolipoprotein B (apo B) inhibition test

Cultured human liver cells (HepG2-cells), which synthesize and secrete low-density lipoproteins, were incubated overnight at 37 °C in a liquid medium containing radioactively labelled leucine. Thus radioactively labelled leucine was incorporated into the apolipoprotein B. The liquid medium was decanted and the apolipoprotein B was isolated by means of a double immunoprecipitation, i.e. first an apolipoprotein B-specific antibody (antibody1) was added to the liquid medium and subsequently a second antibody (antibody2) was added which binds specifically to the apoB-antibody1 complex. The thus formed apoB-antibody1-antibody2 complex precipitated and was isolated by centrifuge. Quantification of the amount of apolipoprotein B synthesized

-25-

5 during the night resulted from measuring the radioactivity of the isolated complex. To measure the inhibiting activity of the test compound, that test compound was added to the liquid medium at different concentrations and the concentration of apolipoprotein B synthesized in the presence of a test compound (concentration apoB(after)) was compared to the concentration of apolipoprotein B which was synthesized in the absence of the test compound (concentration apoB(control)). For each experiment the inhibition of apolipoprotein-B formation was expressed as

10
$$\% \text{ inhibition} = 100 \times (1 - \text{concentration of apoB(after)} / \text{concentration apoB(control)})$$

15 When more experiments were carried out for the same concentration, the median value of the inhibition calculated for these experiments was calculated. IC₅₀-values (concentration of the drug needed to reduce apoB secretion to 50 % of the control) were also computed.

15 Table 13 lists the IC₅₀-values for some of the exemplified compounds of formula (I). Exemplified compounds of formula (I) that are not listed in Table 13, and for which data is available, have an IC₅₀-value of 1×10^{-6} M or more.

20 Table 13

Comp. No.	IC ₅₀ ($\times 10^{-8}$ M)	Comp. No.	IC ₅₀ ($\times 10^{-8}$ M)	Comp. No.	IC ₅₀ ($\times 10^{-8}$ M)
1	9.2	54	7.9	89	51
2	4.7	55	7.8	93	2.7
3	9.1	56	23	94	19
4	26	58	31	95	1.8
5	20	60	4.6	96	4.7
6	12	61	8.1	98	2.0
7	7.9	62	19	99	1.5
8	13	63	4.6	100	2.1
9	11	64	16	101	16
12	19	65	29	102	37
13	51	66	13	105	9.9
15	4.8	67	18	106	88
18	4.1	68	8.1	107	4.5
22	7.1	69	2.6	108	2.6
23	14	71	12	110	2.7
24	5.8	72	19	111	6.2

-26-

Comp. No.	IC ₅₀ (x 10 ⁻⁸ M)
28	9.7
32	18
33	9.1
35	7.7
37	23
38	6.5
40	2.3
43	11
44	5.1
49	85
50	26
51	4.7
52	25
53	8.4

Comp. No.	IC ₅₀ (x 10 ⁻⁸ M)
73	18
74	14
75	12
76	2.4
77	7.1
78	5.3
79	4.6
80	7.2
81	4.9
82	3.1
83	1.5
84	2.8
87	6.9
88	45

Comp. No.	IC ₅₀ (x 10 ⁻⁸ M)
112	98
113	3.0
114	5.3
115	5.7
116	5.8
117	1.6
118	9.1
119	4.6
121	14
122	8.8
123	7.4
126	14
128	18
130	14

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

5 "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

10 Example 8 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

20

-27-

Example 9 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules,

5 each comprising 20 mg of the A.I..

Example 10 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and

10 thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinyl-pyrrolidone (Kollidon-K 90) in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose (Avicel) and 15 g hydrogenated vegetable oil (Sterotex). The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active

15 ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG) in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose (Ethocel 22 cps) in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml

20 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109) and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

25

Example 11 : Injectable solution

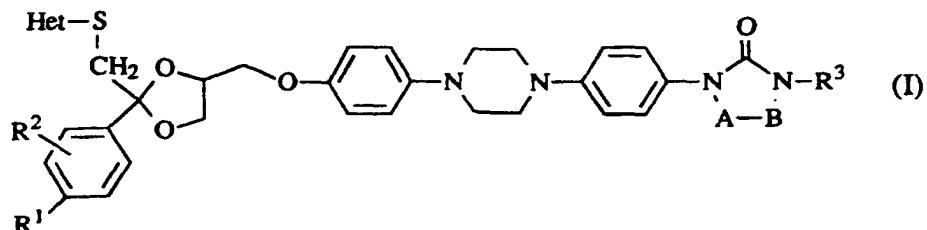
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution

30 was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Claims

1. A compound of formula

5



10 a *N*-oxide, a stereochemically isomeric form, or a pharmaceutically acceptable acid addition salt thereof, wherein A and B taken together form a bivalent radical of formula :

15

- N=CH- (a),
- CH=N- (b),
- CH₂-CH₂- (c),
- CH=CH- (d),
- C(=O)-CH₂- (e),
- CH₂-C(=O)- (f),

20

in the bivalent radicals of formula (a) or (b) the hydrogen atom may be replaced by C₁-6alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C₁-6alkyl;

R¹ is hydrogen, C₁-6alkyl or halo;

R² is hydrogen or halo;

R³ is hydrogen; C₁-8alkyl; C₃-6cycloalkyl; or C₁-8alkyl substituted with hydroxy, oxo, C₃-6cycloalkyl or aryl;

25

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁-6alkyl, hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C₁-6alkyl, hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁-6alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁-6alkyl, hydroxy,

30

C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁-6alkyl, hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)amino; oxadiazole substituted with one or two substituents selected from C₁-6alkyl,

-29-

hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁-6alkyl, hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C₁-6alkyl, hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁-6alkyl, hydroxy, C₁-6alkyloxy, trihalomethyl, amino, mono- or di(C₁-6alkyl)amino, aryl is phenyl or phenyl substituted with C₁-6alkyl or halo.

5

10 2. A compound according to claim 1 wherein R¹ is chloro or fluoro.

15 3. A compound according to claim 1 wherein R¹ is methyl.

4. A compound according to any one of claims 1 to 3 wherein the bivalent radical -A-B- is -N=CH- or -CH=N-, wherein one hydrogen atom is optionally replaced by a C₁-6alkyl.

20 5. A compound according to any of claims 1 to 4 wherein R³ is butyl, pentyl or cyclopentyl.

25 6. A compound according to claim 1 wherein the compound is
cis-4-[4-[4-[(2-(4-chlorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one;
cis-2-[4-[4-[(2-(4-chlorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(1-methylpropyl)-3H-1,2,4-triazol-3-one;
cis-2-[4-[4-[(2-(4-fluorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4-cyclopentyl-2,4-dihydro-3H-1,2,4-triazol-3-one;

30

35

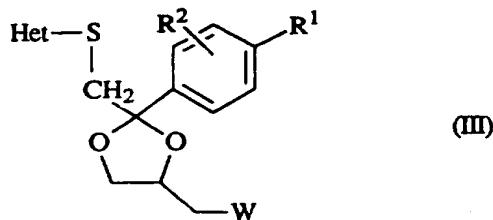
30 2,4-dihydro-3H-1,2,4-triazol-3-one;
cis-2-[4-[4-[(2-(4-chlorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-pentyl-3H-1,2,4-triazol-3-one;
cis-4-(1-ethylpropyl)-2-[4-[4-[(2-(4-fluorophenyl)-2-[[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one; a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

-30-

7. A pharmaceutical composition containing a pharmaceutically acceptable carrier and as an active ingredient a therapeutically effective amount of a compound as claimed in any of claims 1 to 6.

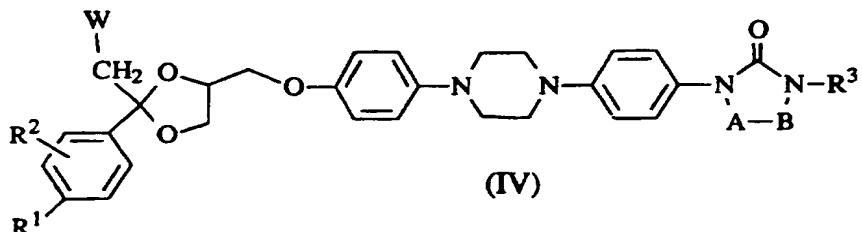
5 8. A process of preparing a pharmaceutical composition as claimed in claim 7, wherein a therapeutically effective amount of a compound as claimed in any of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.

10 9. An intermediate of formula



15 an acid addition salt or a stereochemically isomeric form thereof, wherein R¹, R² and Het are as defined in claim 1 and W is an appropriate leaving group, such as, halo or a sulfonyloxy group.

10. An intermediate of formula



20 20 an acid addition salt or a stereochemically isomeric form thereof, wherein R¹, R², R³, A-B are as defined in claim 1 and W is an appropriate leaving group, such as, halo or a sulfonyloxy group.

25 11. A compound as claimed in any one of claims 1 to 6 for use as a medicine.

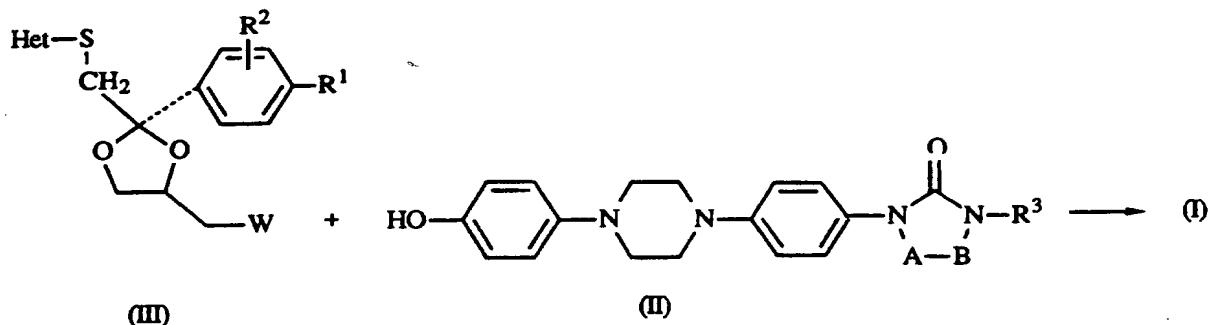
12. A compound as claimed in any one of claims 1 to 6 for use as a medicine useful in the treatment of hyperlipidemia.

30 13. A process for preparing a compound of formula (I) as defined in claim 1, characterized in that:

a) an intermediate of formula (II), wherein -A-B and R³ are as defined in claim 1, is O-alkylated with an intermediate of formula (III), wherein R¹, R² and Het are as

-31-

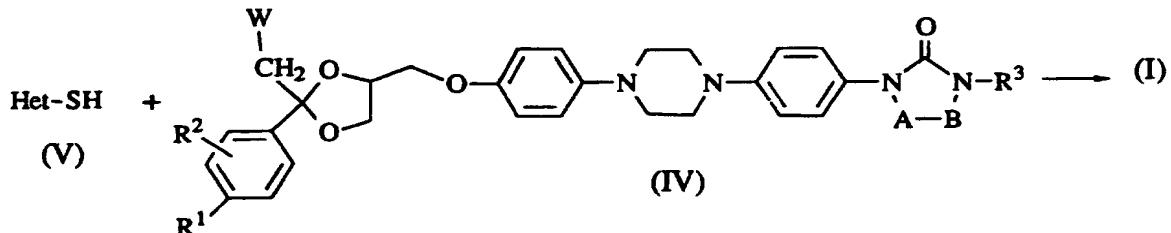
defined in claim 1 and W is an appropriate leaving group such as halo or a sulfonyloxy leaving group,



5

b) an intermediate of formula (V), wherein Het is defined as in claim 1, is reacted with an intermediate of formula (IV), wherein R^1 , R^2 , R^3 , $-\text{A}-\text{B}-$ are as defined in claim 1 and wherein W is an appropriate leaving group such as halo or a sulfonyloxy leaving group;

10



15

or optionally converting the compounds of formula (I) into each other by a functional group transformation reaction; and, if desired, converting a compound of formula (I) into a therapeutically active non-toxic acid addition salt, or conversely, converting an acid addition salt into a free base form with alkali; and / or preparing N -oxide or stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 95/04111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/14 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 006 711 (JANSSEN PHARMACEUTICA NV) 9 January 1980 cited in the application ---	
X	CHEMICAL ABSTRACTS, vol. 106, no. 9, 2 March 1987 Columbus, Ohio, US; abstract no. 67320e, INEKE S.A. '1,2,4-Triazole derivative' page 614; see abstract & ES,A,548 091 -----	10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

18 January 1996

Date of mailing of the international search report

01.02.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentiaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

Intell. al Application No

PCT/EP 95/04111

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0006711	09-01-80	US-A-	4218458	19-08-80
		US-A-	4267179	12-05-81
		AT-T-	5479	15-12-83
		AU-B-	528095	14-04-83
		AU-B-	4816079	03-01-80
		CA-A-	1149386	05-07-83
		EP-A, B	0006712	09-01-80
		JP-A-	1211561	24-08-89
		JP-C-	1502228	28-06-89
		JP-A-	55011578	26-01-80
		JP-B-	63053192	21-10-88
		JP-C-	1497396	16-05-89
		JP-A-	55011579	26-01-80
		JP-B-	63044752	06-09-88
		LU-A-	88218	03-02-94
		US-A-	4313953	02-02-82
		US-A-	4368200	11-01-83
		AT-T-	5140	15-11-83
		BG-B-	60430	31-03-95
		SU-A-	1069625	23-01-84

